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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/576,568 | 01/03/2007 | Susan J. Knox | STAN-333 (S03-309) | 3872 |

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| EXAMINER | |
|---|---|
| CHOI, FRANK I | |
| **ART UNIT** | **PAPER NUMBER** |
| 1616 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/576,568 | KNOX ET AL. | |
| | Examiner | Art Unit | |
| | FRANK I. CHOI | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11/22/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4,6,8-11,15 and 19-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,8-11,15 and 19-33* is/are rejected.

7)☐ Claim(s) ___ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2,4, 6, 8-11, 15, 19-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stiefel et al. (US Pat. 6,656,509) in view of the Applicant's admission, Lemelson et al. (US Pat. 4,665,897), Gorun (US Pat. 6,511,971), Hehr et al. and Abdullaev et al..

The claimed invention is directed to a method of treating a neoplastic disease in a subject by administering inorganic selenium salt and radiation therapy where the administering of the inorganic selenium compound and radiation therapy provides for a synergistic effect in treating the neoplastic disease and radiation therapy is administered to the subject after administering the inorganic selenium compound.

Stiefel et al. discloses a method for producing a synergistic cytotoxic effect on a cancer cell in a patient being treated for cancer by contact the cell with at least one salt of SeO2 and a cytostatic agent, where the administration can be simultaneous, separate or sequential, where the cancer is prostatic carcinoma (Claim 1, Claim 6). It is disclosed that a preferred salt of SeO2 is Na2SeO3 (Column 6, lines 1, 2). It is disclosed that a preferred concentration of selenium or a selenium compound is in a range of 0.1 mg/kg body weight to 0.3 mg/kg body weight and that application can be oral or intravenous (Column 9, lines 28-40).

The Applicant acknowledges that prostate cancer cells can be resistant to apoptosis which plays a role in local and distant disease progression following conventional therapy, such as radiotherapy (Specification, paragraph 0003). It is acknowledged that selenite is capable of inhibiting cell growth and inducing apoptosis in a variety of human cancer cell lines in vitro, inhibit tumor growth of breast and ovarian cancer cells in vivo, and that the induction of apoptosis is mediated by a redox mechanism involving induction of oxidative stress via superoxide formation and lowered intracellular GSH levels (Specification, paragraph 0006).

Lemelson et al. disclose the use of antibodies which target tumor tissue and contain nuclide which can be rendered radioactive by a beam of neutron to generate radiation at the cite of cancerous tissue, such as tumors, thereby destroying the cancerous tissues (Column 10, lines 19-68).

Gorun disclose treatment of tumors with photodynamic sensitizers which produce singlet molecular oxygen and destroys the cancerous tissue (Column 11, lines 14-40).

Hehr et al. disclose administration of 400 micrograms of sodium selenite after every course irradiation of the rectal tumor region and lymph nodes (Abstract).

Abdullaev et al. disclose that sodium selenite given parenterally to mice and racts with sarcoma M-1, Guerin carcinoma, Walker carcinosarcoma, lymphosarcoma and Ehrlich ascites tumors inhibited tumor growth and that antineoplastic activity was enhanced when sodium selenite activity was combined with radiation (Abstract).

Stiefel et al. disclose a method for producing a synergistic cytotoxic effect on a cancer cell in a patient being treated for cancer by contact the cell with at least one salt of SeO2 and a cytostatic agent, where the administration can be simultaneous, separate or sequential, where the

cancer is prostatic carcinoma, the preferred salt of SeO2 is Na2SeO3, the preferred concentration of selenium or a selenium compound is in a range of 0.1 mg/kg body weight to 0.3 mg/kg body weight and that application can include oral or intravenous application. The difference between Stiefel et al. and the claimed invention is that Stiefel et al. does not expressly disclose the use of inorganic selenite, radiation therapy or reactive oxygen species (ROS)-inducing therapy, administration of radiation therapy within 6 hours after administration of the inorganic selenium compound, or the combination of intravenous inorganic selenium and radiation therapy. However, the prior art amply suggests the same as Steifel et disclose that sodium selenite is a preferred source of selenium; the applicant acknowledges that radiotherapy is used to treat prostate cancer; Lemelson discloses use of radiation therapy using neutron beams to active nuclides species at the site of the tumor; Gorun discloses that photodynamic sensitizers which produce singlet molecular oxygen are used to destroy cancerous tissue; Hehr et al. disclose administration of 400 micrograms of sodium selenite after every course irradiation of the rectal tumor region and lymph nodes; and Abdullaev et al. disclose that sodium selenite given parenterally to mice and racts with sarcoma M-1, Guerin carcinoma, Walker carcinosarcoma, lymphosarcoma and Ehrlich ascites tumors inhibited tumor growth and that antineoplastic activity was enhanced when sodium selenite activity was combined with radiation. As such, one of ordinary skill in the art would have expected that the combination of sodium selenite, including intravenously, with other methods of treatment of cancers and tumors would be effective in treating cancers and tumors such as prostate cancer, including where radiation therapy is administered after inorganic selenium administration.

The Examiner has duly considered the Applicant's arguments but deems them unpersuasive.

The Examiner has considered the declaration filed on 10/7/2009 and working examples in the Specification. It does not appear from either the declaration or working examples that there is any evidence showing synergy with radiotherapy. The area under the curve for both LAPC-4 and B PC-3 as between the control, sodium selenite alone, radiation therapy alone and combination appears to be additive rather than synergistic. See Figure 1 of the declaration. Since the prior art specifically discloses the administration of inorganic selenium prior to a round of radiation therapy, the claims do not exclude administration of inorganic selenium during or after radiation therapy, only sodium selenite was tested at specified amounts and the data shows clear differences between different tumor cell lines, the evidence, even if it shows synergy, is not commensurate in scope with the claimed invention as the claims include an unspecified amount of inorganic selenium, are not limited to the type of inorganic selenium, are not limited to the type of cancer or cancer cell line and/or do not exclude concurrent or post-radiation treatment with inorganic selenium. Further, the fact that sodium selenite did not radiosensitize normal cells is not unexpected. See Rodemann et al. (sodium selenite was radioprotective to normal cells but not carcinoma cells). Furthermore, no comparison is made between post-, pre- or concurrent radiation/selenium administration.

The Applicant argues that no reference discloses administering of radiation therapy within 6 hours after administering the inorganic selenium compound. However, it would be readily apparent to one of ordinary skill in the art that administration of inorganic selenium can occur prior to, concurrently or after administration of radiation therapy. As such, it is well

within the skill of one of ordinary skill in the art to administer radiation therapy after administering the inorganic selenium compound at various time intervals as desired depending on effectiveness in treating the cancer, including within a 6 hour time period. The Applicant has not provided evidence showing that administration of radiation therapy within 6 hours after administration of inorganic selenium exhibit unexpected activity against cancer much less synergistic activity.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

A translation of Hehr et al. and Rodemann et al. is provided with this office action.

## Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. The Examiner maintains a flexible schedule, however, the Examiner may generally be reached Monday, Tuesday, Wednesday and Thursday, 6:00 am – 4:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Johann R. Richter, can be reached at (571)272-0646. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frank Choi
Patent Examiner
Technology Center 1600
February 12, 2011

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616